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Title: Prospective evaluation of minimal residual disease in patients with previously untreated Waldenstrom Macroglobulinemia (WM) undergoing treatment with Bendamustine, Rituximab and Acalabrutinib – a BRAWM study analysis

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Affiliations: 1. Sunnybrook Health Sciences Centre, 2. Sunnybrook Research Institute 3. Health Sciences North 4. Queen Elizabeth II Health Sciences Centre 5. Tom Baker Cancer Centre 6. McGill University Health Centre 7. Ottawa Health Research Institute 8. BC Cancer 9. Cross Cancer Institute 10. Juravinski Cancer Centre 11. CHU de Québec – Université Laval 12. Adaptive Biotechnologies 13. University Health Network

Background:
BRAWM is a Phase II clinical trial studying the effects of fixed-duration therapy of six 28-day cycles of bendamustine and rituximab in combination with one year of 100 mg acalabrutinib twice daily in previously untreated patients with WM. Although minimal residual disease (MRD) has been significantly associated with clinical outcomes in various aggressive and indolent lymphomas, its association in patients with WM is not established.

Aims:
In this interim analysis, we describe the MRD rates in peripheral blood (PB) and bone marrow (BM) and association with baseline characteristics of participants enrolled in the BRAWM trial.

Methods:
This study has enrolled 62 participants to meet its primary objective of 59 evaluable participants with a clinical response assessment. MRD samples are collected for all enrolled participants at screening, cycle 7, 12 and month 18. Assessment is performed on samples from PB and BM (aspirate sample preferred, biopsy acceptable). Samples of >2 ml of PB and ≥1 ml of BM aspirate are collected and frozen at -80°C, then shipped in cryo-shippers from participating Canadian centers to Adaptive Biotechnologies (Seattle, Washington, USA) for analysis using the clonoSEQ assay, a next generation DNA sequencing (NGS) of immune receptor sequences (sensitivity threshold 10^{-6}). Pre-treatment samples are calibrated and used as the baseline comparator to future time points. MRD rates and changes over time (log10 reduction) are reported using descriptive statistics. Logistic regression analysis was used to determine baseline variables and treatment characteristics associated with achieving MRD negativity.

Results:
In available PB samples for participants reaching cycle 7, 23/31 (74%) were MRD negative, 17/20 (85%) at cycle 12, and 7/8 (87.5%) at month 18 **(Figure 1A)**. Similarly, in available BM samples for participants at cycle 7, 3/30 (10%) were MRD negative, 2/20 (10%) at cycle 12, and 2/7 (29%) at month 18 **(Figure 1B)**. Results from Fisher's exact test show no association between PB and BM MRD results at cycle 7 (p=0.76), cycle 12 (p=1.00) or month 18 (p=1.00).

From baseline sequence levels, there was a median log reduction of 4.42 (IQR 1.32) by cycle 7 in PB, 4.11 (IQR 1.25) by cycle 12, and 4.06 (IQR 0.81) by month 18 **(Figure 2A)**. In BM, there was a median 2.80 log reduction (IQR 1.80) by cycle 7, 2.78 (IQR 1.69) by cycle 12, and 3.06

(IQR 3.04) by month 18 (**Figure 2B**). On univariate and multivariate logistic regression analyses, no baseline demographic features (age, beta2-microglobulin, LDH, albumin, hemoglobin, platelet count, serum IgM, percentage bone marrow involvement or IPSS-WM risk score) were associated with MRD negativity in PB or BM at cycles 7 or 12.

Discussion:

In this interim analysis, a majority of patients are achieving MRD negativity in the PB, with increasing MRD negativity in BM over time. Longer follow-up of this trial will examine associations of MRD with clinical outcomes. Data from additional participants and follow up will be available for the IWWM-12 meeting.

Figures:

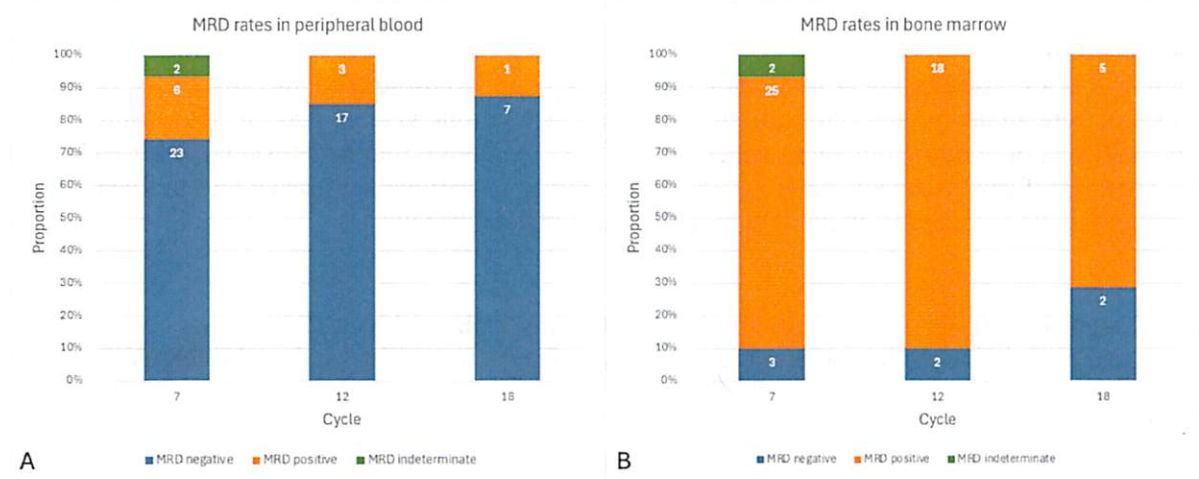

Figure 1. Proportion of patients achieving MRD negativity at cycle 7 (combination therapy for cycles 1-6) cycle 12 (monotherapy for cycles 7-12) and month 18 (no therapy from months 12-18) in the **(A)** peripheral blood and **(B)** bone marrow.

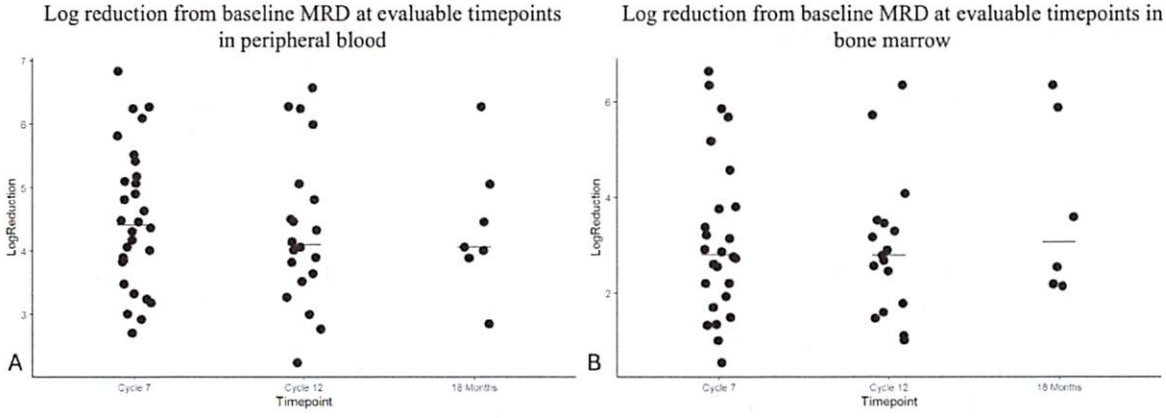

Figure 2. Distribution of MRD log reduction at cycles 7(combination therapy for cycles 1-6), 12 (monotherapy for cycles 7-12) and month 18 (no therapy from months 12-18) in **(A)** peripheral blood and **(B)** bone marrow.

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July 08, 2024

Dear IWWM Young Investigators Awards committee members,

Re-Dr. Adam Suleman

It is my pleasure to write this letter of reference on behalf of Dr. Adam Suleman in support of his application for a Young Investigator travel award to allow Adam to attend the IWWM-2024 and to present our abstract entitled, "Prospective evaluation of minimal residual disease in patients with previously untreated Waldenstrom Macroglobulinemia (WM) undergoing treatment with Bendamustine, Rituximab and Acalabrutinib – a BRAWM study analysis".

Adam is starting a Lymphoma fellowship and is enrolled in the Clinician Investigator Program at the University of Toronto while he completes his Masters of Science in Clinical Epidemiology. He is hoping to pursue a career in academic medicine as a clinician investigator.

Adam has already successfully published 13 first-author publications and prepared the initial draft of the submitted abstract which was then reviewed by all co-authors. Adam joined the BRAWM research team in February 2024 with a keen interest in analysis of MRD data, a novel contribution to the field. He assisted in designing the statistical analyses for this abstract and will continue as a member of the BRAWM team until completion of the study.

Attending IWWM-12 would provide Adam with an opportunity to attend talks by world-renowned speakers, and allow him to further his career as a clinician investigator with a focus on lymphoproliferative disorders. Presentation of his work would allow for discussions around methodology and assist in planning important further analyses. Attending this workshop would allow Adam to further his academic interests as he plans to pursue further training in lymphoproliferative disorders in Canada and abroad.

Please do not hesitate to reach out to me with any additional questions.

Sincerely,

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